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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
LONG, SCOTT

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,071	LI ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8 and 15-39* is/are pending in the application.

4a) Of the above claim(s) *17-20 and 22-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 15-16, 21 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/5/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/12/2008 has been entered.

Claim Status

Claims 1, 3-8 and 15-39 are pending. Claim 1 is amended. Claims 37-39 are newly added. Claims 2 and 9-14 are cancelled. Claims 17-20 and 22-36 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-8, 15-16, 21 and 37-39 are under current examination.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 5 August 2008 consisting of 1 sheet(s) is/are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit as a 371 of PCT/US03/31097 (filed 10/01/2003) which claims benefit of 60/415,319 (filed 10/01/2002). The applicant submitted an oath on 3/24/2005, which was not executed in accordance with there 37 CFR 1.66 or 37 CFR 1.68. The applicant was notified of this in the DO/EO filed 8/1/2005. Since the instant application is a National Stage Application, rather than a standard US non-provisional application, the application was not afforded the filing date 3/24/2005 (when the specification, claims, and drawings were submitted). Rather, the instant application has been granted the filing date of 9/30/2005, which is the date on which a properly executed oath was received. Because receipt of the properly executed oath completed filing of the National Stage application within the 30 month period for filing of the National Stage application of PCT/US03/31097, the instant application has been granted the benefit date, 1 October 2002 from provisional application 60/415,319.

Response to Arguments - Claim Rejections 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-8, 15-16, and 21 remain rejected under 35 USC 102(a/e) as anticipated by Van Meir et al. (WO02/26192).

Applicant's arguments (Remarks, page 12) and claim amendments filed 15 September 2008 have been fully considered but they are unpersuasive.

The applicant argues that Van Meir et al. do not teach each and every limitation of the instant claims. The applicant particularly argues that Van Meir do not teach the newly added limitations directed to "wherein the adenovirus gene is selected from the group consisting of an E1B gene , an E2A gene , an E2B gene and an E4 gene."

Contrary to the applicant's assertion, Van Meir et al. teach each and every limitation of the instant claims. In particular, Van Meir et al. teach the limitations regarding conditional expression of adenoviral genes, and specifically teach conditional expression of E1B. Van Meir et al. teach, "recombinant adenoviruses were able to express constitutively (Ad-CMV-E1) or conditionally (HYPR-Ad1) E1A and E1B gene products." (page 34, lines 1-2 and Fig. 6). Van Meir et al. teach the newly added

limitation, “wherein the adenovirus gene is E1B." Therefore, the examiner considers the applicant’s arguments unpersuasive.

Accordingly, the examiner hereby maintains the rejection of claims 1, 3-8, 15-16, and 21 under 35 USC 102(a/e) as anticipated by Van Meir et al.

The examiner reiterates the instant rejection below:

Claims 1, 3-8, 15-16, and 21 are rejected under 35 USC 102(a/e) as anticipated by Van Meir et al. (WO02/26192).

Claim 1 is directed to an adenovirus vector comprising an adenovirus gene and a transgene, each under the transcriptional control of a transcriptional regulatory element (TRE) comprising a minimal promoter and a hypoxia responsive element (HRE), wherein the adenovirus gene is selected from the group consisting of an E1B gene , an E2A gene , an E2B gene and an E4 gene, wherein the transgene is a suicide gene selected form the group consisting of a TNF-α gene , a Trail gene, a Bax gene, an HSV-tk gene, a cytosine deaminase gene, a p450 gene and a diphtheria toxin gene, an s-Flt1 gene and an ex-Flt gene.

BASIC INVENTIVE CONCEPT: Van Meir et al. teach, “a recombinant virus genetically engineered to have an hypoxia-responsive element, or a multiplicity of such elements, operably linked to a promoter which is operably linked to a gene or genes which regulate or modulate replication of the virus or encode a therapeutic molecule.” (page 7, lines 18-21). Van Meir et al. further describe the recombinant virus as “a recombinant replication-competent adenovirus” and “an hypoxia/HIF-dependent replicative adenovirus” (page 9, lines 10 and 13). Van Meir et al. teach an adenovirus

containing the CMV minimal promoter, hypoxia-response elements, and the E1 gene (page 28, Figure at line 1).

EACH GENE UNDER CONTROL OF HYPOXIC PROMOTER: Van Meir et al. teach, "a recombinant virus genetically engineered to have an hypoxia-responsive element, or a multiplicity of such elements, operably linked to a promoter which is operably linked to a gene or genes which regulate or modulate replication of the virus or encode a therapeutic molecule." (page 7, lines 18-21). Van Meir et al. clearly indicate that both (1) genes required for viral replication and (2) therapeutic genes can be placed under control of promoters comprising hypoxia responsive elements. Van Meir et al. demonstrate a specific embodiment of this type: "a viral construct comprising an hypoxia-dependent replicative adenovirus (HYPR-Ad(s)) that expresses an anti-angiogenic factor under hypoxic conditions (HYPRA-Ad)" (page 13, lines 26-28). Furthermore, Van Meir et al. teach "a plurality of genes can be expressed in response to hypoxia" (page 20, lines 4-5). Van Meir et al. teach "molecular strategy underlying the design of virus mediated gene therapy systems is to deliver a gene which will inhibit tumor cell growth (e.g., controlling cell cycle or apoptosis), kill the cell (suicide gene), or induce an immune response (imrnunotherapy)." (page 2, lines 16-18). Van Meir et al. also teach that thymidine kinase is one of the therapeutic suicide genes which can be used in their invention (page 19, lines 28-29 through page 20, line 1). Van Meir et al. teach, "recombinant adenoviruses were able to express…conditionally (HYPR-Ad1) E1A and E1B gene products." (page 34, lines 1-2). The examiner concludes that Van Meir et al envisioned an embodiment of their invention in which both (1) the adenovirus

gene, E1B, and (2) the thymidine kinase gene would be under the control of a hypoxic promoter.

Claim 3 is directed to the adenovirus vector of claim 1, further comprising a second adenovirus gene under the transcriptional control of the TRE. Van Meir et al. teach, "recombinant adenoviruses were able to express … conditionally (HYPR-Ad1) E1A and E1B gene products. " (page 34, lines 1-2). See also Figure 6.

Claim 4 is directed to the adenovirus vector of claim 1, wherein the minimal promoter is selected from the group consisting of the cytomegalovirus (CMV) minimal promoter, the human β-actin minimal promoter, the human EF2 minimal promoter, and the adenovirus E1B minimal promoter. Van Meir et al. teach an adenovirus "containing the CMV minimal promoter and the E1 gene" (page 12, line 1).

Claim 5 is directed to the adenovirus vector of claim 4, wherein the CMV minimal promoter comprises SEQ ID NO: 1. Van Meir et al. teach an adenovirus "containing the CMV minimal promoter" (page 12, line 1).

Claim 6 is directed to the adenovirus vector of claim 1, wherein the HRE is derived from the human vascular endothelial growth factor (VEGF) promoter. Van Meir et al. teach, "based on this information, EPO and VEGF HRE's were chosen for the design and testing of a hypoxia-responsive promoter" (page 19, lines 1-2).

Claim 7 is directed to the adenovirus vector of claim 6, wherein the HRE comprises SEQ ID NO: 2. Van Meir et al. teach "the VEGF [HRE] sequence… CCACAGTGC TACGTGGGCT CCUCAGGTC CTCTT" which is 100% identical to SEQ ID NO:2 of the instant application.

Claim 8 is directed to the adenovirus vector of claim 7, wherein the HRE comprises five tandem copies of SEQ ID NO: 2. See Van Meir et al., Figure 2, where up to 6 tandem copies of HRE are shown and page 10-11 for detailed description of figure.

Claim 15 is directed to a composition comprising the adenovirus vector of claim 1. Van Meir et al. teach, "compositions of the invention comprise a recombinant virus genetically engineered to have an hypoxia-responsive element, or a multiplicity of such elements, operably linked to a promoter which is operably linked to a gene or genes which regulate or modulate replication of the virus or encode a therapeutic molecule." (page 7, lines 18-21).

Claim 16 is directed to the composition of claim 15, further comprising a pharmaceutically acceptable carrier. Inherently, any aqueous solution of the adenoviral composition of claim 15 would be a pharmaceutically acceptable carrier.

Claim 21 is directed to a host cell comprising the adenovirus vector of claim 1. Van Meir et al. teach, "expression of recombinant viral gene products in transfected cells under hypoxic and normoxic conditions.... adenoviruses, U251MG and LN-229 cells were infected with the Ad-CMV-E1 and HYPR-Ad1" (page 33, lines 17-29).

Accordingly, Van Meir et al. anticipated the instant claims.

Therefore, the examiner hereby maintains the rejection of claims 1-8, 15-16, and 21 under 35 USC 102(a/e) as anticipated by Van Meir et al. (WO02/26192) for the reasons of record and the comments above.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 37 is rejected under 35 U.S.C. 103(a) as being obvious over Van Meir et al. (WO02/26192).

Claim 37 is directed to an adenovirus vector comprising two adenovirus genes and a transgene, each under the transcriptional control of a transcriptional regulatory element (TRE) comprising a minimal promoter and a hypoxia responsive element (HRE), wherein the adenovirus gene is selected from the group consisting of an E1B gene , an E2A gene , an E2B gene and an E4 gene, wherein the transgene is a suicide gene selected form the group consisting of a TNF-α gene , a Trail gene, a Bax gene, an HSV-tk gene, a cytosine deaminase gene, a p450 gene and a diphtheria toxin gene, an s-Flt1 gene and an ex-Flt gene.

BASIC INVENTIVE CONCEPT: Van Meir et al. teach, "a recombinant virus genetically engineered to have an hypoxia-responsive element, or a multiplicity of such elements, operably linked to a promoter which is operably linked to a gene or genes which regulate or modulate replication of the virus or encode a therapeutic molecule." (page 7, lines 18-21). Van Meir et al. further describe the recombinant virus as "a recombinant replication-competent adenovirus" and "an hypoxia/HIF-dependent replicative adenovirus" (page 9, lines 10 and 13). Van Meir et al. teach an adenovirus containing the CMV minimal promoter, hypoxia-response elements, and the E1 gene (page 28, Figure at line 1).

EACH GENE UNDER CONTROL OF HYPOXIC PROMOTER: Van Meir et al. teach, "a recombinant virus genetically engineered to have an hypoxia-responsive element, or a multiplicity of such elements, operably linked to a promoter which is operably linked to a gene or genes which regulate or modulate replication of the virus or encode a therapeutic molecule." (page 7, lines 18-21). Van Meir et al. clearly indicate

that both (1) genes required for viral replication and (2) therapeutic genes can be placed under control of promoters comprising hypoxia responsive elements. Van Meir et al. demonstrate a specific embodiment of this type: "a viral construct comprising an hypoxia-dependent replicative adenovirus (HYPR-Ad(s)) that expresses an anti-angiogenic factor under hypoxic conditions (HYPRA-Ad)" (page 13, lines 26-28). Furthermore, Van Meir et al. teach "a plurality of genes can be expressed in response to hypoxia" (page 20, lines 4-5). Van Meir et al. teach "molecular strategy underlying the design of virus mediated gene therapy systems is to deliver a gene which will inhibit tumor cell growth (e.g., controlling cell cycle or apoptosis), kill the cell (suicide gene), or induce an immune response (immunotherapy)." (page 2, lines 16-18). Van Meir et al. also teach that thymidine kinase is one of the therapeutic suicide genes which can be used in their invention (page 19, lines 28-29 through page 20, line 1). Van Meir et al. teach, "recombinant adenoviruses were able to express…conditionally (HYPR-Ad1) E1A and E1B gene products." (page 34, lines 1-2).

DEFICIENCIES: Van Meir et al. teaches the general idea of adenovirus vectors in which both (1) two adenovirus genes, (E1A and E1B), and (2) the thymidine kinase gene would be under the control of a hypoxic promoter. Additionally, Van Meir et al. teach "Using standard genetic engineering methods, any suitable promoter can be linked to HRE, which are then linked to a gene(s) in a particular virus that regulates or modulates virus replication. A variety of genes and/or their products are known to those skilled in the art that regulate or modulate viral replication." (page 18, lines 2-5). Van Meir et al. specifically uses E1A as an example of such genes. However, Van Meir et

al. do not specifically teach the adenovirus genes E2A, E2B, or E4 can be among those genes regulated by hypoxia-responsive promoters. However, Meir et al. teach "E1B 55K, in conjunction with adenovirus E4orf6 gene product has two functions during viral production" (page 19, lines 23-24).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time of the invention was made to modify the teachings of Van Meir to construct an adenovirus comprising the two adenovirus genes, E1B and E4, each under the control of a hypoxia-responsive promoter, further comprising the suicide gene, thymidine kinase also under control of a hypoxia-responsive promoter.

The person of ordinary skill in the art would have been motivated to make that modification because Van Meir et al. suggest that any viral gene that regulates virus replication could be used in their invention and specifically mentions that E1B and E4 are such genes in adenovirus.

An artisan would have expected success, because Van Meir et al. demonstrates a specific embodiment of adenovirus comprising E1A and E1B operably linked to a hypoxic promoter. Therefore, a skilled artisan would expect substituting other adenovirus genes which control viral replication for either of these genes would be successful.

Therefore the adenovirus as taught by Van Meir et al would have been *prima facie* obvious over the adenovirus of the instant application.

Claim 38 is rejected under 35 U.S.C. 103(a) as being obvious over Van Meir et al. (WO02/26192) in view of Shibata et al. (International Journal of Radiation Oncology Biology Physics. 1998; 42(4): 913-916).

Claim 38 is directed to an adenovirus vector comprising an adenovirus gene and a transgene, each under the transcriptional control of a transcriptional regulatory element (TRE) comprising a minimal promoter and a hypoxia responsive element (HRE), wherein the adenovirus gene is selected from the group consisting of an E1B gene , an E2A gene , an E2B gene and an E4 gene, wherein the transgene is a suicide gene selected form the group consisting of a TNF-α gene , a Trail gene, a Bax gene, an HSV-tk gene, a cytosine deaminase gene, a p450 gene and a diphtheria toxin gene, an s-Flt1 gene and an ex-Flt gene, wherein the minimal promoter is selected from the group consisting of the human β-actin minimal promoter, the human EF2 minimal promoter, and the adenovirus E1B minimal promoter.

BASIC INVENTIVE CONCEPT: Van Meir et al. teach, "a recombinant virus genetically engineered to have an hypoxia-responsive element, or a multiplicity of such elements, operably linked to a promoter which is operably linked to a gene or genes which regulate or modulate replication of the virus or encode a therapeutic molecule." (page 7, lines 18-21). Van Meir et al. further describe the recombinant virus as "a recombinant replication-competent adenovirus" and "an hypoxia/HIF-dependent replicative adenovirus" (page 9, lines 10 and 13). Van Meir et al. teach an adenovirus containing a minimal promoter, hypoxia-response elements, and the E1 gene (page 28, Figure at line 1).

EACH GENE UNDER CONTROL OF HYPOXIC PROMOTER: Van Meir et al. teach, "a recombinant virus genetically engineered to have an hypoxia-responsive element, or a multiplicity of such elements, operably linked to a promoter which is operably linked to a gene or genes which regulate or modulate replication of the virus or encode a therapeutic molecule." (page 7, lines 18-21). Van Meir et al. clearly indicate that both (1) genes required for viral replication and (2) therapeutic genes can be placed under control of promoters comprising hypoxia responsive elements. Van Meir et al. demonstrate a specific embodiment of this type: "a viral construct comprising an hypoxia-dependent replicative adenovirus (HYPR-Ad(s)) that expresses an anti-angiogenic factor under hypoxic conditions (HYPRA-Ad)" (page 13, lines 26-28). Furthermore, Van Meir et al. teach "a plurality of genes can be expressed in response to hypoxia" (page 20, lines 4-5). Van Meir et al. teach "molecular strategy underlying the design of virus mediated gene therapy systems is to deliver a gene which will inhibit tumor cell growth (e.g., controlling cell cycle or apoptosis), kill the cell (suicide gene), or induce an immune response (imrnunotherapy)." (page 2, lines 16-18). Van Meir et al. also teach that thymidine kinase is one of the therapeutic suicide genes which can be used in their invention (page 19, lines 28-29 through page 20, line 1). Van Meir et al. teach, "recombinant adenoviruses were able to express…conditionally (HYPR-Ad1) E1A and E1B gene products." (page 34, lines 1-2).

DEFICIENCIES: Van Meir et al. teaches the general idea of adenovirus vectors in which both (1) an adenovirus genes, (E1A and E1B), and (2) the thymidine kinase gene would be under the control of a transcriptional regulatory element comprising a

minimal promoter and hypoxic response elements. Van Meir et al. teach an adenovirus containing a minimal promoter, hypoxia-response elements, and the E1 gene (page 28, Figure at line 1). However, Van Meir et al. do not specifically teach the minimal promoters can be selected from the group consisting of human β-actin minimal promoter, the human EF2 minimal promoter, and the adenovirus E1B minimal promoter.

However, Shibata et al. teach "the application of multiple copies of the HREs [hypoxia-responsive elements] and an E1b minimal promoter appears to have the advantage of great improvement in hypoxia responsiveness." (Abstract).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time of the invention was made to modify the teachings of Van Meir to incorporate the teachings of Shibata et al., where a resulting adenovirus gene and suicide gene are under the control of E1B minimal promoter and hypoxia-responsive elements.

The person of ordinary skill in the art would have been motivated to make that modification because Shibata et al. suggest combining hypoxia-responsive elements and an E1b minimal promoter greatly improve hypoxia responsiveness.

An artisan would have expected success, because Shibata et al. suggest that the Van Meir et al. adenovirus could have improved hypoxia responsiveness.

Therefore the adenovirus as taught by Van Meir et al would have been *prima facie* obvious over the adenovirus of the instant application.

Claim 39 is rejected under 35 U.S.C. 103(a) as being obvious over Van Meir et al. (WO02/26192) in view of Shibata et al. (International Journal of Radiation Oncology Biology Physics. 1998; 42(4): 913-916).

Claim 39 is directed to an adenovirus vector comprising two adenovirus genes and a transgene, each under the transcriptional control of a transcriptional regulatory element (TRE) comprising a minimal promoter and a hypoxia responsive element (HRE), wherein the adenovirus gene is selected from the group consisting of an E1B gene , an E2A gene , an E2B gene and an E4 gene, wherein the transgene is a suicide gene selected form the group consisting of a TNF-α gene , a Trail gene, a Bax gene, an HSV-tk gene, a cytosine deaminase gene, a p450 gene and a diphtheria toxin gene, an s-Flt1 gene and an ex-Flt gene, wherein the minimal promoter is selected from the group consisting of the human β-actin minimal promoter, the human EF2 minimal promoter, and the adenovirus E1B minimal promoter.

BASIC INVENTIVE CONCEPT: Van Meir et al. teach, "a recombinant virus genetically engineered to have an hypoxia-responsive element, or a multiplicity of such elements, operably linked to a promoter which is operably linked to a gene or genes which regulate or modulate replication of the virus or encode a therapeutic molecule." (page 7, lines 18-21). Van Meir et al. further describe the recombinant virus as "a recombinant replication-competent adenovirus" and "an hypoxia/HIF-dependent replicative adenovirus" (page 9, lines 10 and 13). Van Meir et al. teach an adenovirus containing a minimal promoter, hypoxia-response elements, and the E1 gene (page 28, Figure at line 1).

EACH GENE UNDER CONTROL OF HYPOXIC PROMOTER: Van Meir et al. teach, "a recombinant virus genetically engineered to have an hypoxia-responsive element, or a multiplicity of such elements, operably linked to a promoter which is operably linked to a gene or genes which regulate or modulate replication of the virus or encode a therapeutic molecule." (page 7, lines 18-21). Van Meir et al. clearly indicate that both (1) genes required for viral replication and (2) therapeutic genes can be placed under control of promoters comprising hypoxia responsive elements. Van Meir et al. demonstrate a specific embodiment of this type: "a viral construct comprising an hypoxia-dependent replicative adenovirus (HYPR-Ad(s)) that expresses an anti-angiogenic factor under hypoxic conditions (HYPRA-Ad)" (page 13, lines 26-28). Furthermore, Van Meir et al. teach "a plurality of genes can be expressed in response to hypoxia" (page 20, lines 4-5). Van Meir et al. teach "molecular strategy underlying the design of virus mediated gene therapy systems is to deliver a gene which will inhibit tumor cell growth (e.g., controlling cell cycle or apoptosis), kill the cell (suicide gene), or induce an immune response (imrnunotherapy)." (page 2, lines 16-18). Van Meir et al. also teach that thymidine kinase is one of the therapeutic suicide genes which can be used in their invention (page 19, lines 28-29 through page 20, line 1). Van Meir et al. teach, "recombinant adenoviruses were able to express…conditionally (HYPR-Ad1) E1A and E1B gene products." (page 34, lines 1-2).

DEFICIENCIES: Van Meir et al. teaches the general idea of adenovirus vectors in which both (1) an adenovirus genes, (E1A and E1B), and (2) the thymidine kinase gene would be under the control of a transcriptional regulatory element comprising a

minimal promoter and hypoxic response elements. Regarding the use of two adenoviral genes, Van Meir et al. teach "Using standard genetic engineering methods, any suitable promoter can be linked to HRE, which are then linked to a gene(s) in a particular virus that regulates or modulates virus replication. A variety of genes and/or their products are known to those skilled in the art that regulate or modulate viral replication." (page 18, lines 2-5). Van Meir et al. specifically uses E1A as an example of such genes. However, Van Meir et al. do not specifically teach the adenovirus genes E2A, E2B, or E4 can be among those genes regulated by hypoxia-responsive promoters. However, Meir et al. teach "E1B 55K, in conjunction with adenovirus E4orf6 gene product has two functions during viral production" (page 19, lines 23-24). Regarding the minimal promoter, Van Meir et al. teach an adenovirus containing a minimal promoter, hypoxia-response elements, and the E1 gene (page 28, Figure at line 1). However, Van Meir et al. do not specifically teach the minimal promoters can be selected from the group consisting of human β-actin minimal promoter, the human EF2 minimal promoter, and the adenovirus E1B minimal promoter.

However, Shibata et al. teach "the application of multiple copies of the HREs [hypoxia-responsive elements] and an E1b minimal promoter appears to have the advantage of great improvement in hypoxia responsiveness." (Abstract).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time of the invention was made to modify the teachings of Van Meir to construct an adenovirus comprising the two adenovirus genes, E1B and E4, each under the control of a hypoxia-responsive promoter, further comprising the suicide gene, thymidine kinase

also under control of a hypoxia-responsive promoter. Additionally, it would have been obvious to the person of ordinary skill in the art at the time of the invention was made to modify the teachings of Van Meir to incorporate the teachings of Shibata et al., where a resulting adenovirus gene and suicide gene are under the control of E1B minimal promoter and hypoxia-responsive elements.

The person of ordinary skill in the art would have been motivated to make that modification because Shibata et al. suggest combining hypoxia-responsive elements and an E1b minimal promoter greatly improve hypoxia responsiveness.

An artisan would have expected success, because Shibata et al. suggest that the Van Meir et al. adenovirus could have improved hypoxia responsiveness. An artisan would have expected success, because Van Meir et al. demonstrates a specific embodiment of adenovirus comprising E1A and E1B operably linked to a hypoxic promoter. Therefore, a skilled artisan would expect substituting other adenovirus genes which control viral replication for either of these genes would be successful.

Therefore the adenovirus as taught by Van Meir et al would have been *prima facie* obvious over the adenovirus of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Scott Long/

Patent Examiner, Art Unit 1633